REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 28-32, 34-37 and 41-43 have been canceled without prejudice and Claims 33, 38-39, 44, 46 and 47 have been amended to clarify what Applicants have always regarded as their invention.

Claims 33, 38-40 and 44-47 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003 and kindly direct all future correspondence to the address indicated, *i.e.*, to:

CUSTOMER NO. 35489
Ginger R. Dreger
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Information Disclosure Statement

Applicants respectfully thank the Examiner for considering the Information Disclosure Statements filed on September 11, 2002 and November 7, 2002.

Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code, and the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph (Enablement)

Claims 28-47 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 3 of the instant Office Action). The Examiner alleges that "the specification does not teach any significance or functional characteristics of the PRO1759 polynucleotide (SEQ ID NO:373) or polypeptide (SEQ ID NO:374). The specification also does not disclose any methods or working examples that indicate the polynucleotides and polypeptide of the instant invention are involved in any activity."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 and renders the rejection of these claims moot. Applicants further submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1759 polynucleotide.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office

personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Utility – Application of Standard

Applicants rely on the gene amplification data for priority and to establish patentable utility for the PRO1780 polynucleotide. Further, the Examiner has admitted that the instant application that the nucleic acid encoding the PRO1780 polypeptide is amplified in three lung and colon tumors (HF-000840, HF-000795 and HF-001296). (See page 6 of the instant Office Action).

The Examiner asserts that the Examiner "is unable to find, either in the specification or in the art, an explanation of how ΔCt values are calculated, nor what the significance of such are." (See page 7 of the instant Office Action).

In response, Applicants submit that it is well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 7 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

Applicants respectfully submit that the specification discloses that the nucleic acids encoding PRO1759 had ΔCt value of > 1.0, which is **more than 2-fold increase**, in at least 3 of the tumors listed in Table 8.

It is also well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-

time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1759 is a useful target for therapeutic intervention in lung and colon tumors.

Further, the Examiner asserts that "[t]he data presented in the specification were not corrected for aneuploidy." Thus, the Examiner concludes, "A slight amplification of a gene does not *necessarily* mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid."

In response, Applicants respectfully submit a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants respectfully submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker.

The Examiner contends that "PRO1759 tested slightly positive in only 3 out of 52 lung or colon tumor samples" and concludes that this does not indicate that PRO1759 is a diagnostic probe for lung or colon cancer. The Examiner further quotes Hittelman who teaches that "damaged, *pre-cancerous* lung epithelium is often aneuploid" and asserts that "[t]he gene amplification assay does not provide a comparison between the lung tumor sample and normal lung epithelium, and thus it is not clear whether PRO1759 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium."

Applicants respectfully submit that teachings of Hittelman *et al.* suggest that the chronic exposure to carcinogens leads to outgrowth of abnormal clones associated with chromosomal

instability. In fact, Hittelman *et al.* show that an increase in chromosome number is a common characteristic of cancerous and pre-cancerous epithelial cells and therefore, increase in chromosome number or gene amplification is useful as a marker for a cancerous or pre-cancerous state. Hence, Applicants respectfully submit that whether a pre-cancerous or tumor sample were analyzed, the showing of DNA amplification of PRO1759 gene would still be significant, since it would lead to the diagnosis of either a pre-cancerous state or a cancerous state, which is the utility asserted here.

Furthermore, Applicants submit that the amplification of the nucleic acids in even one lung or colon tumor provides specific and substantial utility for the nucleic acid as a diagnostic marker of the type of lung or colon tumor in which it was amplified. Applicants submit that the tumors listed in Table 8 are not similar tumors from different patients, but various types/classes of lung and/or colon tumors at different stages. Accordingly a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung/colon tumor, whereas absence of amplification would be non-conclusive.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1759 gene. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polynucleotides.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1759 polypeptide. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101.

Claim Rejection - 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, allegedly since "the claimed invention is not supported by either a specific and substantial utility or a well established

utility." In particular the Examiner asserts that "the specification does not teach any variant, fragment, or derivative of PRO1759 polypeptide other than the full-length amino acid sequence of SEQ ID NO:374. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, and derivatives recited in the claims." (See instant Office Action, page 9).

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot. In addition, Claim 46 has been amended to recite, "An isolated host cell comprising the vector of Claim 44."

Applicants respectfully submit that as amended, the claims are not broadly drawn to all variants and fragments of the PRO1759 nucleic acid. Indeed, based on the instant disclosure and the advanced knowledge in the art at the time of filing, one skilled in the art would know exactly how to make and use the claimed nucleic acids for the diagnosis of lung and colon tumors; for example, by using diagnostic methods based on hybridization to such amplified sequences.

Further, Applicants respectfully submit that based on the teachings of Example 143 and the general knowledge available in the art at the priority date of the invention, one skilled in the art would be able to practice the claimed invention in its full scope without any undue experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-33, 36-37 and 41-47 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional

applications, Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 and amendments to Claims 33 and 44 render the rejection of these claims moot.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 28-33, 36-37 and 41-47 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that Claims 28-33, 36-37 and 41-47 are rendered indefinite because of the phrases "extracellular domain" and "extra cellular domain ... lacking its associated signal sequence." The Examiner further alleges that Claim 42 is rendered indefinite because of the phrase "stringent conditions".

Applicants submit that the cancellation of Claims 28-32, 35-37 and 41-43 renders the rejection of these claims moot.

Furthermore, since the terms "extracellular domain" and "extra cellular domain ... lacking its associated signal sequence" are no longer present in Claim 33 (and, as a consequence, those claims dependent from the same), the rejection is believed to be moot, and should be withdrawn.

Claim Rejections – 35 U.S.C. §102

Claims 28-30 and 41-47 are rejected under 35 U.S.C. § 102(e) as being anticipated by LeFleur *et al.* (U.S. Patent No. 6,569,992), with effective priority date of February 9, 1998. The Examiner alleges that LeFleur *et al.* disclose a nucleic acid that is 91.6% identical to the nucleic acid of SEQ ID NO:373.

Applicants submit that the cancellation of Claims 28-30 and 41-43 renders the rejection of these claims moot. Furthermore, Claim 44 (and, as a consequence, those claims dependent from the same) has been amended to be dependent on Claim 33. Thus, the rejection of Claims 44-47 is believed to be moot, and should be withdrawn.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C65**)

Respectfully submitted,

Date: February 3, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

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